Investigation of drug absorption from the gastrointestinal tract of man. III. metoprolol in the colon

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1 The colonic absorption of metoprolol was indirectly evaluated by measuring drug appearance in plasma following intravenous, jejunal or colonic infusion in six healthy volunteers. Plasma concentrations of α -hydroxymetoprolol and urinary excretion of the main metabolites were also measured.

2 Plasma profiles of metoprolol after colonic and jejunal perfusion were similar, and the relative bioavailabilities of the drug from these two regions of the gut were not significantly different.

3 The concentrations of α -hydroxymetoprolol, the major metabolite in plasma, were similar after jejunal and colonic perfusion, but higher than those observed after intravenous administration.

4 The percentage of the dose recovered in urine over 24 h as two metabolites was not significantly influenced by the route of administration.

Keywords metoprolol drug absorption colon

Introduction

The potential therapeutic advantages of rate-controlled dosage forms with extended durations of release may be compromised by poor or unpredictable drug absorption from the colon. The rate and extent of absorption may be influenced by physiological factors such as mucosal and bacterial metabolism, water re-absorption from the lumen, changes in the surface area and permeability of the mucous layer of the epithelium, etc. An acceptable and reproducible systemic availability from rate-controlled dosage forms can only be achieved if drug absorption is relatively uniform throughout the greater part of the gastrointestinal tract.

In previous studies (Jobin *et al.*, 1985; Vidon *et al.*, 1985) we have shown that the β -adrenoceptor antagonist, metoprolol, is not absorbed in the stomach but is uniformly absorbed from each segment of the small intestine in man. In the present study the drug's

colonic absorption was investigated after perfusion of a saline solution to six healthy volunteers using a variation of an existing intubation technique. A direct evaluation of absorption by measuring drug removal from the colonic lumen was not considered feasible. Hence, it was estimated indirectly by comparing plasma concentrations of the parent drug and urinary excretion of its main metabolites after intravenous (i.v.), jejunal and colonic perfusion of a metoprolol tartrate solution.

Methods

Subjects

Six healthy volunteers (five male, one female, aged 23–29 years), with no symptomatology or history of gastrointestinal or cardiovascular

disease were selected. They were given an explanation of the study and gave written informed consent before participating. The volunteers were required not to take any medication during the 8 days preceding the study, and to refrain from smoking for 12 h before, and throughout the period of blood sampling.

Study procedure

The three treatments were administered over a 10 day period. On day 1, metoprolol tartrate was administered by i.v. infusion at a rate of 0.59 ± 0.01 mg/min (mean $\pm$ s.d.) over 150 min; the total amount given varied slightly because of minor differences in infusion rate, the mean amount $\pm$ s.d. being 88.7 ± 1.1 mg. On day 8, in the afternoon, a double-lumen tube was introduced through the nose into the intestine. In the morning of day 9, its distal end was positioned under radiological control at a site close to the duodeno-jejunal junction. A metoprolol solution (NaCl 140 mmol, KCl 5 mmol, metoprolol tartrate 130 mg/l) was then perfused at a flow rate of 4.50 ± 0.25 ml/min over 150 min (mean dose 87.5 ± 5.4 mg). On day 10, the tube was repositioned with its end located in the caecum, and the perfusion procedure was repeated (mean flow rate: 4.50 ± 0.28 ml/min, mean dose $\pm$ s.d.: 84.1 ± 8.6 mg).

Sample collection

Blood samples (5 ml) were withdrawn into heparinized tubes before and at 20, 40, 60, 80, 100, 120, 150 min, and 3, 3.5, 4, 5, 6, 8 and 10 h after initiating drug administration. Plasma was separated by centrifugation. Urine was collected before dosing and during 24 h thereafter. The volume was measured and suitable aliquots taken. All samples were stored at -20°C until analysed.

Analytical methods

The concentrations of metoprolol and its main metabolite in plasma, α -hydroxymetoprolol (Borg *et al.*, 1975; Regårdh & Johnsson, 1980), were determined simultaneously by an h.p.l.c. method (Lecaillon *et al.*, 1984), with a limit of quantitation of 10 ng/ml (35 nmol/l). The concentrations of the major metabolite in urine, the 4-phenylacetic acid derivative (Borg *et al.*, 1975), were determined by an h.p.l.c. method (Godbillon & Duval, 1984), the limit of quantitation being 5 $\mu\text{g/ml}$. This method, which involves only dilution of urine with water

before injection, appeared suitable for the simultaneous assay of the α -hydroxy and 4-phenylacetic acid metabolites with satisfactory precision and accuracy.

Pharmacokinetic treatment and statistical evaluation

The fraction of the dose available from jejunum or colon was calculated as:

$$F = \frac{\text{AUC}_{(\text{j or c})}}{\text{AUC}_{(\text{i.v.})}} \times \frac{\text{dose}_{(\text{i.v.})}}{\text{dose}_{(\text{j or c})}}$$

where $\text{AUC}_{(\text{j})}$, $\text{AUC}_{(\text{c})}$ and $\text{AUC}_{(\text{i.v.})}$ are the areas under the plasma concentration-time curves extrapolated to infinity for jejunal, colonic and i.v. perfusion, respectively. These AUC values were calculated as:

$$\text{AUC} = \text{AUC}_{(0-10)} + \frac{C_{10}}{0.693} \times t_{1/2}$$

where $\text{AUC}_{(0-10)}$ is the area under the curve up to 10 h, calculated by the trapezoidal rule, C_{10} the measured concentration at 10 h, and $t_{1/2}$ the plasma terminal half-life of metoprolol.

As the doses were not identical for each subject in the three treatments, AUC/dose and $C_{\text{max}}/\text{dose}$ ratios were employed for statistical comparison of the data using the *t*-test for paired values.

Results

Plasma profiles

The plasma concentrations of metoprolol after jejunal and colonic perfusion were similar, but significantly lower than those observed after i.v. administration (Figure 1). No significant difference ($P > 0.05$) could be detected between AUC/dose , $C_{\text{max}}/\text{dose}$ (Table 1) and $t_{1/2}$ values for the parent drug in jejunum and colon. The bioavailability of metoprolol from these two regions of the GI tract was also similar (Table 2).

The concentrations of α -hydroxymetoprolol in plasma after perfusion of the drug in jejunum and colon were similar but higher than those observed after i.v. administration (Figure 2). The $\text{AUC}_{(0-10)}/\text{dose}$ and $C_{\text{max}}/\text{dose}$ ratios after jejunal and colonic perfusion were not significantly different ($P > 0.05$), but were both significantly higher ($P < 0.01$ for jejunum, $P = 0.05$ for colon) than after i.v. infusion (Table 1).

Figure 1 Mean plasma concentrations of metoprolol (expressed as nmol/l of free base) after i.v. (●), jejunal (□) and colonic (○) perfusion over a period of 2.5 h (mean doses of metoprolol tartrate: i.v. 88.7 ± 1.1 mg; jejunum 87.5 ± 5.4 mg; colon 84.1 ± 8.6 mg).

Table 1 Apparent pharmacokinetic parameters of metoprolol and α -hydroxymetoprolol in plasma after intravenous, jejunal and colonic perfusion over a period of 2.5 h. AUC/dose: area under the plasma concentration-time curve, corrected for the dose. $C_{\max}$ /dose: observed maximum concentration corrected for the dose.

	Subjects	Metoprolol			α -hydroxymetoprolol		
		i.v.	Jejunum	Colon	i.v.	Jejunum	Colon
AUC/dose* (nmol l ⁻¹ h/ μ mol)	1	30.5	13.4	21.2	1.9	2.2	2.9
	3	20.1	9.6	16.0	2.8	4.5	6.6
	5	28.9	10.2	11.8	4.7	5.8	6.4
	2	18.7	2.9	2.9	3.7	5.3	—
	4	21.8	2.9	2.2	3.8	5.1	4.7
	6	19.9	2.8	3.1	5.0	6.7	7.0
	Mean	23.3	7.0	9.6	3.6	4.9	5.5
$C_{\max}$ /dose (nmol l ⁻¹ / μ mol)	CV (%)	22	67	83	33	31	31
	1	5.0	1.9	1.6	0.3	0.4	0.4
	3	3.2	1.3	1.8	0.4	0.7	1.0
	5	6.1	1.3	1.5	0.6	0.8	1.0
	2	3.7	0.5	0.5	0.5	0.9	—
	4	2.5	0.3	0.3	0.5	0.8	0.7
	6	4.6	0.6	0.6	0.7	1.3	1.1
	Mean	4.2	1.0	1.1	0.5	0.8	0.8
	CV (%)	31	60	64	40	37	37

*AUC extrapolated to infinity for metoprolol
AUC (0–10) for α -hydroxymetoprolol
CV: coefficient of variation

Table 2 Fraction of the dose of metoprolol tartrate available from jejunum and colon compared to intravenous perfusion (calculated from the AUC values corrected for the dose of metoprolol perfused i.v., in jejunum, or in colon over 2.5 h)

Subjects	Jejunum	Colon
1	0.44	0.70
3	0.48	0.79
5	0.35	0.41
2	0.16	0.16
4	0.13	0.10
6	0.14	0.16
Mean	0.28	0.39
s.e. mean	0.06	0.12

Urinary excretion

The percentage of the administered dose recovered in urine over 24 h as the α -hydroxy and 4-phenylacetic acid metabolites was not significantly ($P > 0.05$) influenced by the route of drug administration (Table 3).

Discussion

Plasma profiles of metoprolol

The similarity of the individual plasma profiles

obtained after continuous delivery of metoprolol to the jejunum and colon suggest that this β -adrenoceptor blocker is absorbed at the same rate and to the same extent from the two regions of the human gastrointestinal tract. These findings, together with those from other studies in this series (Jobin *et al.*, 1985; Vidon *et al.*, 1985), indicate that metoprolol is similarly absorbed between the pylorus and the rectum, and there is no selective site of absorption of this drug in the gut. Therefore, metoprolol administered as an oral formulation should be absorbed from any region of the intestine in which it is released.

This conclusion is supported by the similarity in AUC/dose values for *in situ* perfusion in the present study with those recorded by Kendall *et al.* (1980) for conventional or slow-release tablets. Good absorption of metoprolol from the human gut has also been demonstrated by Regårdh *et al.* (1974), using [^3H]-labelled metoprolol; 96% of administered radioactivity was recovered in urine after oral dosing with a solution.

The average fraction of metoprolol tartrate systemically available after jejunum and colon perfusion (Table 2) was within the range of values (0.19–0.54) reported for orally administered doses by Regårdh *et al.* (1974). This indicates that first-pass metabolism of meto-

Figure 2 Mean plasma concentrations of α -hydroxymetoprolol (expressed as nmol/l of free base) after i.v. (●), jejunal (□) and colonic (○) perfusion over a period of 2.5 h (mean doses of metoprolol tartrate: i.v. 88.7 ± 1.1 mg; jejunum 87.5 ± 5.4 mg; colon 84.1 ± 8.6 mg).

Table 3 24-h urinary excretion (% of dose) of α -hydroxymetoprolol and 4-phenylacetic acid, after i.v., jejunal and colonic perfusion over 2.5 h (mean values $\pm$ s.e. mean)

Metabolite	i.v.	Perfusion	
		Jejunum	Colon*
α -hydroxymetoprolol	7.1 $\pm$ 0.9	8.8 $\pm$ 0.6	10.2 $\pm$ 0.8
4-phenylacetic acid	43.6 $\pm$ 3.7	55.2 $\pm$ 3.5	61.1 $\pm$ 5.9

*Means of five subjects (incomplete collection for subject 1)

prolol is similar whether given orally or perfused into the intestine. The apparent elimination half-life of metoprolol was also unaffected by the route of administration, the mean values after i.v., jejunal and colonic perfusion in the present study being in agreement with reported values after i.v. (Regårdh *et al.*, 1974) or oral dosing (Kendall *et al.*, 1980).

The plasma concentrations of metoprolol achieved after i.v. administration were similar for the six subjects. In contrast, plasma profiles of the parent drug after jejunal and colonic perfusion showed a large variability, as indicated by the coefficient of variation of the AUC/dose and C_{max} /dose values (Table 1).

Plasma profiles of α -hydroxymetoprolol

Intravenous perfusion gave rise to lower plasma concentrations of α -hydroxymetoprolol than intestinal delivery. This difference could be attributed to first-pass metabolism in the liver, but the possibility of biotransformation by the gastrointestinal mucosa cannot be excluded. Experiments performed in the dog (Hess *et al.*, 1981) indicated significant loss of drug in the gut lumen or gut wall since the bioavailability of metoprolol perfused in the proximal or distal colon was lower than that after perfusion in the portal vein. Whether this difference is due to gut metabolism or to another rate-limiting absorption phenomenon has not yet been determined.

As judged from the ratio of the mean AUC values, the area under the curve for α -hydroxymetoprolol after jejunal or colonic perfusion was equivalent to that of the parent drug (α -hydroxymetoprolol/metoprolol ratios: 1.01 and 0.93, respectively). These values were comparable to those reported after oral administration of a similar dose of metoprolol contained in an Oros system (Lecaillon *et al.*, 1985) or conventional tablet (Quarterman *et al.*, 1981) under fasting conditions. This indicates that the

different release rates from each formulation do not result in different plasma concentrations of the α -hydroxy metabolite. Therefore, the first-pass effect of metoprolol in doses of 100–200 mg is probably not saturated.

The intersubject variability in AUC of α -hydroxymetoprolol was lower than that of the parent drug, and was of similar magnitude for each perfusion route (Table 1). The proportions of α -hydroxymetoprolol relative to the parent drug were around five times greater for subjects 2, 4 and 6, who could be considered as extensive metabolizers of metoprolol (Lennard *et al.*, 1982).

Urinary excretion of metabolites

The similarity in urinary excretion of α -hydroxymetoprolol after i.v., and jejunal or colonic perfusion indicates that similar amounts were produced over 24 h. The urinary excretion values for α -hydroxymetoprolol and the 4-phenylacetic acid metabolite were comparable to those reported previously with lower doses given i.v. (Hoffman *et al.*, 1980; Borg *et al.*, 1975) or orally as a solution (Borg *et al.*, 1975). They were also comparable to those reported for a similar dose given orally as conventional tablets (Quarterman *et al.*, 1981). The percentage of the dose recovered as these two metabolites in urine over 24 h is therefore not influenced by the route of administration.

In conclusion, this study demonstrates that metoprolol tartrate is absorbed to the same extent and at the same rate from jejunum and colon. This finding, in conjunction with results from other studies in the series, indicate that there is no selective site of absorption of this drug between the pylorus and rectum.

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